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Checkpoint inhibitors in cancer immunotherapy: Cross reactivity of a CTLA-4 antibody and IDO-inhibitor L-1MT in pigs

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Blockade of checkpoint inhibitors has recently shown very convincing results in the treatment of cancer. One key target is CTLA-4, which has been demonstrated to be a potent negative regulator of lymphocyte activation. The treatment with the FDA-approved fully human CTLA-4 monoclonal antibody Ipilimumab increases anticancer T-cell reactivity and overall survival of metastatic cancer patients. Indole-amine 2,3-dioxygenase (IDO) is another checkpoint inhibitor which suppresses T-cell immunity by the depletion of tryptophan in the T-cell microenvironment, and also inhibition of IDO by L-1-Methyltryptophan (L-1MT) has shown promising results in clinical phase I/II studies of human cancer such as epithelial ovarian cancer.

Pre-clinical immune therapeutic studies are usually performed with mice, but Ipilimumab is not reactive with mouse cells. Recent studies indicate that the pig may be a more suitable animal model for studies of immune reactivity due to higher similarity of the immunome between pig and man. This study is part of the CANVACPIG project “Accelerating development of vaccines against cancer with pigs as a large animal model” and investigates the reactivity of a fully human monoclonal anti CTLA-4 antibody and L-1MT on porcine immune cells.

At the genome level, the homology between human and pig CTLA-4 and IDO is 86% and 73%, respectively, while the homology to the mouse is 75% and 63%. Our preliminary in vitro studies indicate that the monoclonal anti CTLA-4 antibody induces a non-specific activation of porcine T cells. This will be further investigated to provide the basis for in vivo studies investigating checkpoint inhibitor blockade in combination with other cancer immunotherapies. Eventually our goal is to establish pigs as an alternative large animal model for development and formulation of new human cancer vaccines.